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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/904,786 | 07/12/2001 | Avi Ashkenazi | 10466/84 | 3015 |

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| EXAMINER | |
|---|---|
| BASI, NIRMAL SINGH | |

| ART UNIT | PAPER NUMBER |
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| 1646 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/904,786 | ASHKENAZI ET AL. | |
| | Examiner | Art Unit | |
| | NIRMAL S. BASI | 1646 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *39-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. Upon further review the finality of the previous office action is withdrawn. The claims are newly rejected for the reason given below.

2. The rejection under 35 USC § 101 for lack of utility is withdrawn in view of applicants arguments filed 11/14/07. Applicants' arguments, pertaining to the rejection of claims 39-43, filed 11/14/07 and 8/29/07, have been fully considered but they have not been found to be persuasive. Applicants' arguments are discussed in the rejection below.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 39-43 are rejected under 35 U.S.C. 112, first paragraph, as lacking enablement for reasons of record and those given below. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants argue compounds which inhibit proliferation of lymphocytes are useful therapeutically where suppression of an immune response is beneficial. However, the ability of the claimed antibody or PRO335 protein to stimulate or inhibit lymphocyte proliferation in the MLR assay does not provide for what specific conditions or for which specific diseases the claimed invention would predictably function for a therapeutic suppression of the immune system. The assertion that the claimed invention could be useful for the treatment of conditions where the enhancement of the immune response would be beneficial is not enabled by the disclosure of the instant specification. The only use

contemplated for the claimed invention is a therapeutic suppression of the immune system. Kahan clearly states that no *in vitro* immune assay predicts or correlates with *in vivo* immunosuppressive efficacy; there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from *in vitro* systems to *in vivo* conditions (Cur. Opin. Immunol. 4: 553-560, 1992; see entire document, particularly page 558, column 2). Piccotti et al. (Transplantation 67: 1453-1460, 1999) demonstrate that IL-12 enhances alloantigen-specific immune function as determined by MLC, but this result *in vitro* does not result in a measurable response *in vivo* (i.e. failure to accelerate allograft rejection) (see page 1459). Campo et al. (Biological Trace Element Res. 79: 15-22, 2001) demonstrate that while zinc suppresses alloreactivity in MLC, it does not decrease T-cell proliferation *in vitro* nor produce immunosuppressive effects *in vivo*. Therefore, while the art recognizes the MLR assay as accepted for screening for immunosuppressive molecules in vitro with a general, which is art recognized for being generally predictive of their in vivo effectiveness, this biological activity does not correlate to use of the claimed protein in a therapeutically effective manner, as the asserted use of the claimed invention proposes.

The enablement of claimed invention is based on Assay 74 disclosed in the specification. Assay 74 states, "Positive increases over control are considered positive with increases of greater than or equal to 180% being preferred. However, any value greater than control indicates a stimulatory effect for the test protein." Applicants further look for support in the declaration of Sherman Fong. Dr. Fong generally discusses that the MLR assay is widely used and discloses IL-22 as a known immune stimulant, which has been shown to stimulate T-cell proliferation in the MLR assay. Dr. Fong further goes on to state on page 3, paragraph 10, "It is my considered scientific opinion that a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with at least 180% of the control, as specified in the present application, is expected to have the type of activity as that exhibited by Il-2". The

examiner agrees with the statement that that a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with at least 180% of the control, as specified in the present application, could possibly have the type of activity as that exhibited by Il-2. The problem is that PRO335 has not been disclosed to have T-cell proliferation activity in the MLR assay with at least 180% of the control. The exact value is not disclosed. The number of samples tested is not disclosed. The stastical analysis applied to anayse the results is not disclosed. The disclosure only states that the results were positive. A result of 100.1% is positive, just as a result of 180% is positive. Lets turn to assay 79, which is similar to assay 74, but where any decrease is considered to be a positive result for an inhibitory compound, with decreases of less than or equal to 80% being preferred. Based on the prior art and even Applicants preferences, values around the control are less preferable, because clear statements such as those by Dr. Fong that the MLR assay of the present invention with at least 180% of the control could possibly have the type of activity as that exhibited by Il-2 could not be made otherwise. Could this statement be made if the activity was 100.1%, for example? The specification does not provide any values or data for the proteins tested in the assay. The specification does not provide any statistics for the values measured in the assay. The specification provides no information at all regarding the results of the assay except that certain proteins tested positive and the statement that "any value greater than control indicates a stimulatory effect for the test protein". The value over control is important, Even Dr. Fong highlights the value of 180%.

The questions are: What specific disease states would benefit by therapeutic enhancement of stimulation of lymphocyte proliferation by use of the claimed antibody or PRO335? What do the results of the MLR assay of Example 74, using PRO335, disclose about the disease state that could be treated by stimulation of lymphocyte proliferation? As disclosed by the examples provided by applicant different compounds effect the stimulation of lymphocyte proliferation to different degrees and in turn have different therapeutic effects. Il-2

arguments natural killer cell activity in patients with AIDS and is recommended for advanced renal cell carcinoma. Il-15 which was found to be at least as potent and effective as IL-2 in the MLR assay prolongs survival of lymphoma-bearing mice and suppresses pulmonary metastases induced by injection of sarcoma. Il-21 found to enhance the proliferation of T cells in an MLR assay potentially inhibits B16 melanoma tumors. Alpha-GalCer demonstrated to enhance the T-cell response in an MLR assay inhibits tumor metastasis in liver or lung. Therefore, based on the varied effects of the compounds that have stimulated the lymphocyte proliferation assay no prediction as to the specific therapeutic value of PRO335 cannot be made without further experimentation. The compounds that tested positive in the MLR assays discussed above did not produce the same amount of stimulation in the assays and did not result as therapeutics for the same disease states.

The MLR assay is an accepted *in vitro* model for screening immunosuppressive agents for use in the prevention of graft-versus-host disease and graft rejection. However, the assay must be evaluated as it pertains to the asserted use of the claimed invention, which is for therapeutic enhancement of the immune response of an individual. If the claimed invention is to be used for therapeutic enhancement of the immune response of an individual, the question to ask is how are the results of the MLR assay related to the asserted utility of the claimed invention? Fung-Leung et al. cited by Applicants (see IDS 10/30/06) for support that the MLR assay is used for identifying immunomodulatory compounds. However, the disclosure of Fung-Leung et al. is much more than what is in the instant specification and the immunosuppressive effect being measured was specifically for alloantigens. Several controls were run, as were determinations that the inhibitory effect was not related to cell toxicity. Lastly, Fung-Leung et al. concluded that the results of the multiple MLR assays and controls "suggests its potential use as an immunosuppressant in clinical therapy" (page 364, first sentence). It was not until the compound was tested in an *in vivo* mouse model that the authors declared it an immunosuppressant. Therefore, the

conclusions reached by Fung-Leung et al. are based on much more experimental data, assays and testing that that provided in the instant specification and the reference does not support the position that the MLR assay in the instant specification is predictive of use as a therapeutic compound for suppressing the immune response. The results of the MLR assay in the instant specification are merely preliminary, and much more experimentation is necessary for one of ordinary skill in the art to use the claimed invention in the manner disclosed. This experimentation would be considered undue, because until it is performed, the skilled artisan cannot use the claimed invention in the manner disclosed.

Further, no "particular antigen" is identified in the specification; there is no guidance as to how PRO335 could be used to boost the response to any antigen. Current Protocols in Immunology states on p. 3.12.11 that the MLR "only detects dividing cells instead of measuring true effector T-cell function" and that it is "not clear which T cell function is measured in proliferate assays", and further that "the proliferate response should be used solely as a general indicators of T cell reactivity". Data obtained might variously reflect proliferation of CTL, lymphokine producing T cells, or non-activated bystander cells and will be severely affected by the function of non-T cells. Differences in responsiveness in a proliferative assay in part reflect differences in IL-2 production, according to Current Protocols in Immunology. As has been stated previously, the MLR measures the reactivity of one individual to another and is, as Current Protocols in Immunology states, highly variable. Current Protocols in Immunology in fact describes many variables that must be controlled for. In the instant application, no such controls, such as for maximum response or for the inherent variability of individual responses, are provided. There is no indication of the statistical significance of the results. There are no autologous controls. No correlation is provided to any particular *in vivo* function; there is no guidance to indicate that PRO335 could be used to any therapeutic effect for the treatment of diseases such as cancer or HIV. The references cited by Applicant fail to provide compensatory guidance. Steinman and Thurner et al. (cited by applicants on 8/20/04) address the utility of

dendritic cells but not of a stimulatory MLR. Gubler (cited by applicants on 8/20/04) describes the identification of the molecule IL-12 but uses the MLR merely to compare activities, not as the basis for describing a molecule as a therapeutically useful immunostimulant. The subsequent research of Peterson et al. (cited by applicants on 8/20/04) was clearly required to suggest that the molecule could be used in this fashion. Thus, without further guidance correlating the observed stimulatory activity to a particular, useful property, it would require undue experimentation to use PRO335 or the antibody that specifically binds PRO335.

It is noted that no agonistic or antagonistic effect of antibodies on PRO335 as it relates to its effect on a specific disease state is shown in the specification. Also, antibodies that specially bind to PRO335 were not evaluated in the MLR assay. There is no disclosure of which antibodies are "agonistic antibodies" or "antagonistic antibodies" i.e. which epitopes of PRO335 raise "agonistic antibodies, which epitopes of PRO335 raise "antagonistic antibodies. None are known and none are disclosed. Just because an antibody specifically binds to PRO335 does not automatically mean it will act as an agonist or antagonist.

Because the claimed invention is not enabled and does not meet the requirements of 112/1$^{st}$ paragraph for the reasons provided above and the previous office actions.

4. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NIRMAL S. BASI whose telephone number is (571)272-0868. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571-272-0835. The fax

phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nirmal S. Basi/
Examiner, Art Unit 1646

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